

**Citation:**

Brouwer IA, Heeringa J, Geleijnse JM, Zock PL, Witteman JC. Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study. *Am Heart J*. 2006 Apr; 151 (4): 857-862. PMID: 16569549.

**PubMed ID:** [16569549](#)

**Study Design:**

Prospective cohort study.

**Class:**

B - [Click here](#) for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To examine the association between high fish intake and associated intake of n-3 EPA and DHA and risk of incident atrial fibrillation.

**Inclusion Criteria:**

Subjects were male and female inhabitants of Ommoord, Netherlands, age 55 years and older, who participated in the prospective Rotterdam Study and for whom dietary data was available.

**Exclusion Criteria:**

The study was delimited to inhabitants of Ommoord. Individuals younger than 55 years of age and those with atrial fibrillation at baseline or having a history of atrial fibrillation were excluded.

**Description of Study Protocol:****Recruitment**

Inhabitants from Ommoord, Netherlands who were 55 and older were invited to participate. Those who agreed to participate and signed informed consent forms were included in the study.

**Design**

5,184 subjects were interviewed in their home and examined during two visits at the research center for baseline data collection. Follow-up data were obtained during two follow-up rounds, once during the period between July, 1993 to December, 1994 and again from April, 1997 to December, 1999. Subjects were followed through the second follow-up round or until atrial fibrillation, whichever occurred first. Information on health status, medical history, smoking, BMI and blood pressure were obtained at baseline. Dietary assessment was obtained using a self-administered food frequency and followed up with an interview with a trained dietitian. Atrial

fibrillation was assessed with a 10-second, 12-lead ECG, which was analyzed using a modular diagnostic system (MEANS) and verified by blind diagnosis by cardiologists and GP files and hospital records.

### **Statistical Analysis**

Cox proportional hazards analysis was used to examine associations between EPA and DHA intake and the onset of atrial fibrillation and between fish intake and the onset of atrial fibrillation. Hazard ratios were expressed as relative risks (RRs) and were calculated with 95% confidence intervals adjusted for age, sex and energy intake. Additional adjustments were made for presence of diabetes, myocardial infarction, saturated fat intake, alcohol, smoking, blood pressure, HDL-cholesterol and total cholesterol levels at baseline. The analysis were repeated excluding those subjects who had a history of myocardial infarction at baseline.

### **Data Collection Summary:**

#### **Timing of Measurements**

Measurements were made at baseline and during two follow-up rounds, once during the period between July, 1993 and December, 1994 and again from April, 1997 to December, 1999.

#### **Dependent Variables**

Atrial fibrillation was measured by a 10-second 12-lead ECG.

#### **Independent Variables**

- Dietary intake of n-3 EPA and DHA
- Dietary intake of fish.

#### **Control Variables**

- Sex
- Age
- Energy intake
- Diabetes mellitus
- Previous MI
- Blood pressure
- HDL-cholesterol
- Total cholesterol
- Saturated fat intake
- Alcohol intake
- Smoking.

### **Description of Actual Data Sample:**

- *Initial N*: 7,983 subjects participated in the study
- *Attrition (final N)*: 5,184 subjects (2,105 men and 3,079 women) completed the study. 209 subjects were excluded for AF at baseline and 167 were excluded with history of AF
- *Age*: Mean age, 67.4±7.7 years

- *Ethnicity*: Dutch
- *Anthropometrics*: Similar BMI, smoking status, diabetes incidence, blood pressure, blood lipids in all tertiles of EPA and DHA intake
- *Location*: Ommoord, Netherlands.

## Summary of Results:

After a mean follow-up of 6.4 ( $\pm 1.6$  years), 312 subjects developed AF. The tables below show survival free of AF for the tertiles of EPA+DHA and fish intake.

|                             |   | Tertile of EPA+DHA  |                      |                      |
|-----------------------------|---|---------------------|----------------------|----------------------|
|                             |   | <43mg per day (ref) | 43 to 144mg per day  | >144mg per day       |
| <b>Number of Subjects</b>   |   | 1,728               | 1,728                | 1,728                |
| <b>Number of AF Events</b>  |   | 96                  | 111                  | 105                  |
| <b>Incidence per 1,000y</b> |   | 8.6                 | 10.0                 | 9.5                  |
| <b>All Subjects</b>         | <i>RR (adjusted for sex, age, energy intake)</i>                  | 1.0                 | 1.22<br>(0.92,1.61)  | 1.25<br>(0.95, 1.67) |
|                             | <i>RR (adjusted for sex, age, energy plus other confounders *</i> | 1.0                 | 1.22<br>(0.92, 1.61) | 1.18<br>(0.88, 1.57) |

\*Model includes diabetes, alcohol intake, SF intake, smoking, systolic blood pressure, HDL and total cholesterol, previous MI.

Similar RR were observed when only subjects without previous MI were analyzed.

|                             |   | Tertile of Fish Intake |                      |                      |
|-----------------------------|---|------------------------|----------------------|----------------------|
|                             |   | Zero fish (ref)        | Zero to 20g per day  | >20g per day         |
| <b>Number of Subjects</b>   |   | 1,527                  | 2,030                | 1,627                |
| <b>Number of AF Events</b>  |   | 84                     | 124                  | 104                  |
| <b>Incidence per 1,000y</b> |   | 8.4                    | 9.5                  | 10.0                 |
| <b>All Subjects</b>         | <i>RR (adjusted for sex, age, energy intake)</i>                  | 1.0                    | 1.17<br>(0.89,1.54)  | 1.27<br>(0.95, 1.70) |
|                             | <i>RR (adjusted for sex, age, energy plus other confounders *</i> | 1.0                    | 1.07<br>(0.81, 1.42) | 1.17<br>(0.87, 1.57) |

\*Model includes diabetes, alcohol intake, SF intake, smoking, systolic blood pressure, HDL and total cholesterol, previous MI.  
Similar RR were observed when only subjects without previous MI were analyzed.

### Author Conclusion:

Intake of EPA and DHA and fish consumption were not associated with a reduced risk of atrial fibrillation. The findings do not support the anti-arrhythmic effect of n-3 fatty acids.

### Reviewer Comments:

*In this study, the range of n-3 EPA and DHA intake was narrow and the mean intake of fish in this population was approximately one fish meal per week (only half the American Heart Association recommended level).*

### Research Design and Implementation Criteria Checklist: Primary Research

#### Relevance Questions

- |    |   |     |
|----|---|-----|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | Yes |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?   | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?  | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies)  | Yes |

#### Validity Questions

- |      |   |     |
|------|---|-----|
| 1.   | <b>Was the research question clearly stated?</b>  | Yes |
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?   | Yes |
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated?  | Yes |
| 1.3. | Were the target population and setting specified?   | Yes |
| 2.   | <b>Was the selection of study subjects/patients free from bias?</b>   | Yes |
| 2.1. | Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? | Yes |

|           |  |     |
|-----------|--|-----|
| 2.2.      | Were criteria applied equally to all study groups?   | Yes |
| 2.3.      | Were health, demographics, and other characteristics of subjects described?  | Yes |
| 2.4.      | Were the subjects/patients a representative sample of the relevant population?   | Yes |
| <b>3.</b> | <b>Were study groups comparable?</b>   | Yes |
| 3.1.      | Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)  | Yes |
| 3.2.      | Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?   | Yes |
| 3.3.      | Were concurrent controls used? (Concurrent preferred over historical controls.)  | Yes |
| 3.4.      | If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?  | Yes |
| 3.5.      | If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) | N/A |
| 3.6.      | If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?  | N/A |
| <b>4.</b> | <b>Was method of handling withdrawals described?</b>   | Yes |
| 4.1.      | Were follow-up methods described and the same for all groups?  | Yes |
| 4.2.      | Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)  | No  |
| 4.3.      | Were all enrolled subjects/patients (in the original sample) accounted for?  | Yes |
| 4.4.      | Were reasons for withdrawals similar across groups?  | ??? |
| 4.5.      | If diagnostic test, was decision to perform reference test not dependent on results of test under study?   | N/A |
| <b>5.</b> | <b>Was blinding used to prevent introduction of bias?</b>  | Yes |
| 5.1.      | In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?  | N/A |

|           |   |            |
|-----------|---|------------|
| 5.2.      | Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) | Yes        |
| 5.3.      | In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?   | Yes        |
| 5.4.      | In case control study, was case definition explicit and case ascertainment not influenced by exposure status?   | N/A        |
| 5.5.      | In diagnostic study, were test results blinded to patient history and other test results?   | N/A        |
| <b>6.</b> | <b>Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?</b>         | <b>Yes</b> |
| 6.1.      | In RCT or other intervention trial, were protocols described for all regimens studied?  | N/A        |
| 6.2.      | In observational study, were interventions, study settings, and clinicians/provider described?  | Yes        |
| 6.3.      | Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?  | Yes        |
| 6.4.      | Was the amount of exposure and, if relevant, subject/patient compliance measured?   | Yes        |
| 6.5.      | Were co-interventions (e.g., ancillary treatments, other therapies) described?  | No         |
| 6.6.      | Were extra or unplanned treatments described?   | No         |
| 6.7.      | Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?   | Yes        |
| 6.8.      | In diagnostic study, were details of test administration and replication sufficient?  | N/A        |
| <b>7.</b> | <b>Were outcomes clearly defined and the measurements valid and reliable?</b>   | <b>Yes</b> |
| 7.1.      | Were primary and secondary endpoints described and relevant to the question?  | Yes        |
| 7.2.      | Were nutrition measures appropriate to question and outcomes of concern?  | Yes        |
| 7.3.      | Was the period of follow-up long enough for important outcome(s) to occur?  | Yes        |
| 7.4.      | Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?                                       | Yes        |
| 7.5.      | Was the measurement of effect at an appropriate level of precision?   | Yes        |
| 7.6.      | Were other factors accounted for (measured) that could affect outcomes?   | Yes        |
| 7.7.      | Were the measurements conducted consistently across groups?   | Yes        |

|            |  |     |
|------------|--|-----|
| <b>8.</b>  | <b>Was the statistical analysis appropriate for the study design and type of outcome indicators?</b>   | Yes |
| 8.1.       | Were statistical analyses adequately described and the results reported appropriately?   | Yes |
| 8.2.       | Were correct statistical tests used and assumptions of test not violated?  | Yes |
| 8.3.       | Were statistics reported with levels of significance and/or confidence intervals?  | Yes |
| 8.4.       | Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? | No  |
| 8.5.       | Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?                           | Yes |
| 8.6.       | Was clinical significance as well as statistical significance reported?  | Yes |
| 8.7.       | If negative findings, was a power calculation reported to address type 2 error?  | Yes |
| <b>9.</b>  | <b>Are conclusions supported by results with biases and limitations taken into consideration?</b>  | Yes |
| 9.1.       | Is there a discussion of findings?   | Yes |
| 9.2.       | Are biases and study limitations identified and discussed?   | Yes |
| <b>10.</b> | <b>Is bias due to study's funding or sponsorship unlikely?</b>   | Yes |
| 10.1.      | Were sources of funding and investigators' affiliations described?   | Yes |
| 10.2.      | Was the study free from apparent conflict of interest?   | Yes |

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